

RECEIVED

(19) World Intellectual Property
Organization
International Bureau



DEC 28 2004

GENERAL ELECTRIC CO.

(43) International Publication Date
5 August 2004 (05.08.2004)

PCT

(10) International Publication Number
WO 2004/064695 A1

(51) International Patent Classification⁷: A61F 9/007,
A61M 1/00

12065 (US). MALE, Jonathan, Lloyd [GB/US]; 345
State Route 443, Shoharie, NY 12157 (US).

(21) International Application Number:
PCT/US2003/041825

(74) Agents: WINTER, Catherine, J. et al.; Patent Counsel,
General Electric Company, 3135 Easton Turnpike W3C,
Fairfield, CT 06828 (US).

(22) International Filing Date:
18 December 2003 (18.12.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/342,475 16 January 2003 (16.01.2003) US

(71) Applicant (*for all designated States except US*): GEN-
ERAL ELECTRIC COMPANY [US/US]; 1 River Road,
Schenectady, NY 12345 (US).

(84) Designated States (*regional*): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

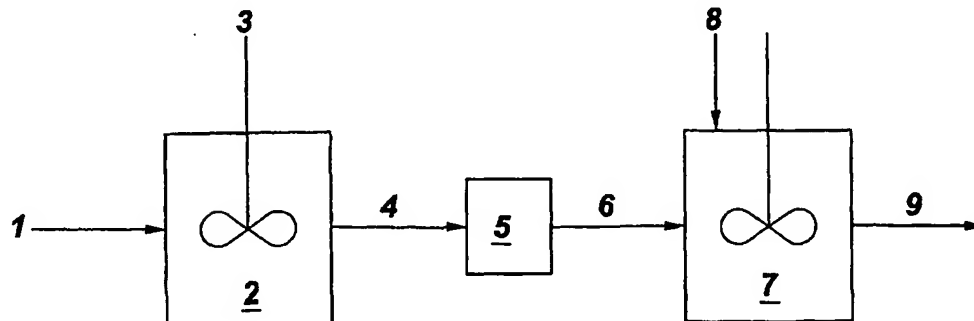
(75) Inventors/Applicants (*for US only*): PRESSMAN,
Eric, James [US/US]; 451 Miller Road, East Greenbush,
NY 12061 (US). OFORI, John, Yaw [GH/US]; 1187
Hillside Avenue, Apt. B36, Niskayuna, NY 12309 (US).
SOLOVEICHIK, Grigori, Lev [RU/US]; 37 Laura
Drive, Latham, NY 12110 (US). MILLS, Ryan, Christo-
pher [US/US]; 1402 Schooner Court, Clifton park, NY

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: BROMINATION OF HYDROXYAROMATIC COMPOUNDS AND FURTHER CONVERSION TO DIHYDROX-
YAROMATIC COMPOUNDS



(57) Abstract: Brominated hydroxyaromatic compounds such as p-bromophenol are prepared by contacting a hydroxyaromatic compound with oxygen and a bromine source such as hydrogen bromide or an alkali metal or alkaline earth metal bromide in an acidic medium, in the presence of elemental copper or a copper compound as catalyst. The brominated product of this reaction may be converted alternately to a dihydroxyaromatic compound such as hydroquinone by hydrolyses, or a dihydroxybiphenyl compound such as 4,4'-dihydroxybiphenyl by reductive coupling.

WO 2004/064695 A1

BEST AVAILABLE COPY

BROMINATION OF HYDROXYAROMATIC
COMPOUNDS AND FURTHER CONVERSION TO
DIHYDROXYAROMATIC COMPOUNDS

BACKGROUND OF THE INVENTION

This invention relates to the reactions of hydroxyaromatic compounds, and more particularly to the conversion of such compounds to brominated derivatives, monocyclic dihydroxyaromatic compounds and dihydroxybiphenyls.

Monocyclic dihydroxyaromatic compounds such as hydroquinone and dihydroxybiphenyls such as 4,4'-dihydroxybiphenyl (hereinafter sometimes simply "biphenol") have numerous uses in the chemical industry. For example, both compounds can be used in polymer preparation, notably in the preparation of polycarbonates, polysulfones and polyimides, especially polyetherimides.

There are various methods for the preparation of hydroquinone and biphenol. As examples of such methods, each compound can be prepared from p-bromophenol, hydroquinone by hydrolysis and biphenol by reductive coupling in the presence of a noble metal catalyst, a base and a reducing agent.

Brominated hydroxyaromatic compounds, as exemplified by p-bromophenol, can be prepared by reaction of the precursor hydroxyaromatic compound with elemental bromine or with various kinds of bromides. For the most part, the use of hydrogen bromide alone is not successful. Auxiliary reagents are required; these may include oxidizing agents, reducing agents, catalysts and/or complexing agents. As a result, the commercial production of bromophenols by reaction of phenols with hydrogen bromide or other simple ionic bromides has, in general, not been pursued.

Normally, chemical plants are set up to produce a single product or group of products in a single reaction or a unitary sequence of reactions. It is thus possible to set up a single set of equipment and use it, on either a batch or continuous basis, permanently to produce the desired product.

Toll producers of chemicals, on the other hand, may utilize a wide variety of equipment, choosing individual items for use depending on the chemical then being produced. To vary the product, they may vary the connections between reactors so as to design a suitable set of equipment for the particular product.

So far as is presently known, the use of a unitary set of equipment to produce two or more widely diverse products is not a commercial alternative.

SUMMARY OF THE INVENTION

The present invention provides a facile method for the preparation of brominated hydroxyaromatic compounds using simple ionic bromides such as hydrobromic acid. Also provided is a method and apparatus for converting the brominated products thus prepared into two separate and diverse classes of chemicals, on an alternating basis. Thus, a first product may be synthesized as needed, after which a second product may be synthesized without any change in the equipment employed.

In a first aspect, the invention is a method for preparing a brominated hydroxyaromatic compound which comprises contacting a hydroxyaromatic compound with oxygen and a bromide source in an acidic medium, in the presence of elemental copper or a copper compound as catalyst.

A second aspect of the invention is a method for converting a hydroxyaromatic compound to useful products which comprises:

(A) brominating said hydroxyaromatic compound to a p-brominated product in a first reaction vessel, and

(B) transferring said p-brominated product to a second reaction vessel and alternately (1) hydrolyzing it to form a p-dihydroxyaromatic compound and (2) reductively coupling it to form a dihydroxybiphenyl compound.

A third aspect is apparatus for conducting chemical reactions, said apparatus comprising:

I. a first reaction vessel adapted for the bromination of a hydroxyaromatic compound to a p-brominated product, and

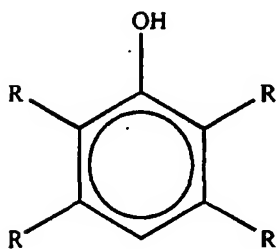
II. a second reaction vessel communicating directly or indirectly with said first vessel, said second vessel adapted for the alternate hydrolysis of said p-brominated product to a dihydroxyaromatic compound and reductive coupling of said p-brominated product to a dihydroxybiphenyl compound.

BRIEF DESCRIPTION OF THE DRAWING

The drawing is a block diagram of the apparatus of the invention.

DETAILED DESCRIPTION; PREFERRED EMBODIMENTS

The common initial reactant for all products obtained according to this invention is a hydroxyaromatic compound, preferably a monocyclic monohydroxyaromatic compound. It may be an unsubstituted hydroxyaromatic compound such as phenol, or a substituted compound provided, however, that the 4-position is unsubstituted and thus available for bromination. Preferred substituents (one or more) are alkyl groups, particularly C₁₋₄ alkyl. Illustrative compounds are those having the formula



wherein each R is independently hydrogen or a substituent, preferably C₁₋₄ alkyl.

Particularly preferred in most instances is phenol, and specific reference will be frequently made to phenol hereinafter. However, homologous compounds such as o- and m-cresol may be substituted for phenol as desired.

According to the first aspect of the invention, the phenol is contacted with oxygen and a bromine compound. The oxygen is employed in stoichiometric excess and may be pure oxygen or may be employed in the form of air or oxygen-enriched air; ordinary air is often preferred. Contact may be with flowing oxygen or air or under pressure, typically up to about 100 atm.

Suitable bromine compounds include hydrogen bromide and bromide salts. Hydrogen bromide may be employed in any form; examples are gaseous HBr, aqueous HBr (hydrobromic acid) and HBr in solution in a polar organic solvent, typically one of the solvents described hereinafter. Bromide salts include alkali metal bromides such as sodium bromide and potassium bromide and alkaline earth metal bromides such as calcium bromide and magnesium bromide. Hydrobromic acid is generally the preferred bromine compound. It may be employed at any concentration, including the commercially available 48% (by volume) aqueous solution.

Said contact is in an acidic medium. Aqueous acidic media including Brønsted acids generally, and particularly including sulfuric acid, phosphoric acid and nitric acid, may be employed; or, if hydrobromic acid is the bromine compound employed, it may serve as the acidic medium. Polar organic solvents may also be present. These may include polar aprotic solvents such as acetonitrile, dimethyl sulfoxide, chloroform and o-dichlorobenzene, as well as protic solvents such as water, acetic acid and excess hydroxyaromatic compound. Acetic acid and acetonitrile are frequently preferred. Mixtures of the foregoing solvents may be employed. It is often preferred that the reaction medium be anhydrous.

Said contact is also in the presence of elemental copper or a copper compound as a catalyst of the bromination reaction. Copper compounds are generally preferred. Examples are cupric sulfate, cupric chloride, cupric bromide, cuprous chloride and cuprous bromide. Cupric bromide is often preferred by reason of its relatively low cost and particular suitability, as contact with hydrobromic acid will usually convert other cupric salts to the bromide.

The bromination reaction may be conducted at a temperature in the range of about 20-150°C, preferably about 60-80°C. Proportions of copper source are most often in the range of about 0.1-30 mole percent of copper based on hydroxyaromatic compound. The molar ratio of ionic bromide to hydroxyaromatic compound is preferably less than 1:1, to minimize conversion to dibromo and more highly brominated compounds; ratios in the range of about 0.2-0.9:1 are typical.

The product of the bromination reaction is usually predominantly the p-bromo compound, with minor amounts of o-bromo compound and dibromo and higher

compounds also being present. Conversion of phenol to bromophenols is, for the most part, at least 40%, "conversion" being defined as total phenol (in weight units or moles) consumed as a percentage of phenol originally present. Selectivity to 4-bromophenol is usually at least 80% and often greater than 90%, "selectivity" meaning moles of the specific product formed as a percentage of moles of phenol consumed.

Separation of the bromophenol compounds prepared according to the invention may be effected by art-recognized methods. Distillation is generally preferred, since there is a difference of more than 40°C between the boiling points of 2-bromophenol (194.5°C) and 4-bromophenol (238°C) and the dibromophenols have even higher boiling points. Distillation may be conducted under reduced pressure to minimize thermal decomposition.

According to the second aspect of the invention, a bromination reaction, which may preferably be but need not be the reaction of the first aspect, is conducted in a first reaction vessel, which may be a conventional tank reactor as used in a batch process or a continuous stirred tank reactor (CSTR) as used in a continuous process. When necessary or appropriate, the bromination product mixture may be transferred from said first vessel to appropriate separation means. The p-brominated product is thence transferred to a second reaction vessel, which may also be a tank reactor or CSTR, for performance of the second step.

The key feature of this aspect is the performance alternately of the hydrolysis and reductive coupling steps. These are alternated as desired to produce the currently desired product; by "alternately" is meant that the hydrolysis and reductive coupling operations are performed in succession as required by product necessities, with switching between the two operations when needed. Both the hydrolysis and the reductive coupling steps may be performed batchwise or continuously, as described hereinabove for the bromination step.

For hydrolysis to a dihydroxyaromatic compound such as hydroquinone (aspect B-1), the bromophenol is contacted with an aqueous base in the presence of a suitable catalyst, typically elemental copper or an oxide thereof, at a temperature of at least

about 75°C and preferably in the range of about 75-150°C. Illustrative conditions are those described in any part of US Patent 1,934,656, the disclosure of which is incorporated by reference herein.

For reductive coupling to a dihydroxybiphenyl compound such as biphenol (aspect B-2), the bromophenol is contacted with a reducing agent such as formic hydrazide in the presence of an aqueous base and a platinum group catalyst, preferably palladium which may be supported on carbon. This reaction may be carried out at temperatures similar to those of the hydrolysis step, typically in the range of about 60-100°C. US Patent 5,177,258 is incorporated by reference herein for its disclosure of typical conditions for the reductive coupling reaction.

A notable feature of reactions B-1 and B-2 is the similarity of the conditions under which they are performed. Both require relatively low temperatures, no higher in general than about 150°C. Both employ aqueous base, most often an alkali metal hydroxide and a metal-containing catalyst. Both can be conducted in either a glass or a metal reaction vessel; if a vessel comprising copper is used for hydrolysis, it may provide enough of that metal to serve as a catalyst.

Thus, it is possible to use the second vessel for either hydrolysis or reductive coupling, with little or no alteration other than cleaning before changing from one reaction to the other. This has the advantage of making it possible to conduct the hydrolysis and reductive coupling reactions on an alternating basis.

Reference is now made to the drawing to help explain the apparatus of the invention. Phenol, hydrobromic acid, copper compound and any solvent employed are introduced at 1 into first reaction vessel 2, which may be a tank reactor, a CSTR, a plug flow reactor or the like. The reactants may be introduced through separate lines or premixed and introduced through a single line.

In vessel 2, the reactants are brought into contact and mixed with the aid of agitator 3, under conditions for preparation of bromophenols. When the reaction has reached substantial completion, the product is withdrawn at 4 and passed into optional separation (e.g., distillation) means 5, where the constituents of the product are

separated and the desired constituent, usually 4-bromophenol, is passed at 6 into second reaction vessel 7 which is equipped with agitator 10.

Depending on the product desired, the constituent introduced at 6 may be contacted at 8 with aqueous base and a copper-containing catalyst under conditions for hydrolysis of bromophenol to hydroquinone, which is removed at 9. When the need for production of hydroquinone has been met, vessel 7 may be cleaned and introduction of constituent at 6 resumed, while reducing agent, aqueous base and platinum group catalyst are introduced at 8. Conditions are established for the reductive coupling of bromophenol to biphenol and its removal at 9. Other equipment suitable for purification of hydroquinone or biphenol may be fed at 9 from vessel 7.

The invention is illustrated by the following examples. All percentages are by weight.

EXAMPLE 1

To a 3-dram vial were charged 1.37 ml (15.56 mmol) of phenol, 0.112 g (0.5 mmol) of cupric bromide, 1.39 ml (12.50 mmol) of 48% hydrobromic acid and 2.20 ml of acetonitrile. The vial was sealed with a cap containing a hole to allow for air flow during the reaction and placed in an aluminum block. The block was placed in a 450-ml autoclave reactor, pressurized to 34.0 atm with air and heated at 65° C for 1 hour. It was then cooled to room temperature and depressurized. The resulting mixture was analyzed by vapor phase chromatographic analysis and shown to contain 7.39% phenol, 28.63% 4-bromophenol, 5.59% 2-bromophenol and 0.68% 2,4-dibromophenol, corresponding to 72% phenol conversion, with 82% 4-bromophenol selectivity and a total monobromophenol selectivity of 98%.

EXAMPLE 2

To a 3-dram vial were charged 1.59 ml (15.39 mmol) of o-cresol, 0.112 g (0.5 mmol) of cupric bromide, 1.48 ml (12.47 mmol) of 48% hydrobromic acid and 1.92 ml of acetonitrile. The vial was sealed and located as in Example 1, pressurized to 34.0 atm with air and heated at 65° C for 1 hour. It was then cooled to room temperature and depressurized. The resulting mixture was analyzed by vapor phase chromatographic analysis and shown to contain 13.23% o-cresol, 27.74% 4-bromo-2-methylphenol and

0.93% 6-bromo-2-methylphenol, corresponding to 56% o-cresol conversion, with 96% 4-bromo-2-methylphenol selectivity and a total monobromophenol selectivity of 99%.

EXAMPLE 3

To a 3-dram vial were charged 1.37 ml (15.56 mmol) of phenol, 0.112 g (0.5 mmol) of cupric bromide, 1.30 ml (6.85 mmol) of a 30% solution of hydrogen bromide in acetic acid and 2.31 ml of acetonitrile. The vial was sealed and located as in Example 1, pressurized to 34.0 atm with air and heated at 65° C for 1 hour. It was then cooled to room temperature and depressurized. The resulting mixture was analyzed by vapor phase chromatographic analysis and shown to contain 14.12% phenol, 19.15% 4-bromophenol and 1.15% 2-bromophenol, corresponding to 44% phenol conversion, with 96% 4-bromophenol selectivity and a total monobromophenol selectivity of 100%.

EXAMPLE 4

An apparatus as shown in the drawing is employed, with each of vessels 2 and 7 being a tank reactor. In vessel 2, the procedure of Example 3 is performed in amounts suitable for commercial production on reagents introduced separately at 1. The product is withdrawn at 4 and distilled in distillation apparatus 5. The 4-bromophenol recovered by distillation is passed at 6 into vessel 7 fabricated of copper.

In a first run, aqueous sodium hydroxide solution is introduced at 8 and the conditions described in Example 1 of US Patent 1,934,656 are maintained. The hydroquinone obtained as product is worked up and isolated as in that example.

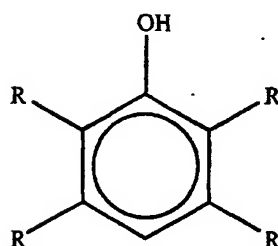
EXAMPLE 5

In a second run following the preparation and isolation of 4-bromophenol as in Example 4, a coupling reaction to produce biphenol is performed in accordance with the general disclosure of US Patent 5,177,258. The reaction employs 1 part of 4-bromophenol in vessel 7 and 2.5 parts of sodium hydroxide, 0.6 part of palladium catalyst (5% by weight on carbon) and 3 parts of formic hydrazide in water, introduced at 8.

While typical embodiments have been set forth for the purpose of illustration, the foregoing descriptions and examples should not be deemed to be a limitation on the scope of the invention. Accordingly, various modifications, adaptations, and alternatives may occur to one skilled in the art without departing from the spirit and scope of the present invention

What is claimed is:

1. A method for preparing a brominated hydroxyaromatic compound which comprises contacting a hydroxyaromatic compound with oxygen and a bromine compound selected from the group consisting of hydrogen bromide and ionic bromide salts in an acidic medium, in the presence of elemental copper or a copper compound as catalyst.
2. A method according to claim 1 wherein said medium is anhydrous.
3. A method according to claim 1 wherein the hydroxyaromatic compound has the formula



wherein each R is independently hydrogen or C₁₋₄ alkyl.

4. A method according to claim 1 wherein the hydroxyaromatic compound is phenol, o-cresol or m-cresol.
5. A method according to claim 4 wherein the hydroxyaromatic compound is phenol.
6. A method according to claim 4 wherein the hydroxyaromatic compound is o-cresol.
7. A method according to claim 1 wherein the bromine compound is hydrogen bromide.
8. A method according to claim 1 wherein the oxygen is provided by air.
9. A method according to claim 1 wherein the copper is provided as cupric bromide, cupric sulfate, cupric chloride, cuprous chloride or cuprous bromide.

10. A method according to claim 9 wherein the copper is provided as cupric bromide.
11. A method according to claim 1 wherein flowing oxygen is employed.
12. A method according to claim 1 wherein oxygen under pressure is employed.
13. A method according to claim 1 wherein a polar organic solvent is also present.
14. A method according to claim 1 wherein the solvent is acetonitrile, dimethyl sulfoxide, chloroform, o-dichlorobenzene, water, phenol, o-cresol, m-cresol, propionic acid or acetic acid.
15. A method according to claim 14 wherein the solvent is acetonitrile or acetic acid.
16. A method according to claim 1 wherein a temperature in the range of about 20-150°C is employed.
17. A method according to claim 1 wherein a molar ratio of ionic bromide to hydroxyaromatic compound less than 1:1 is employed.
18. A method according to claim 1 wherein the proportion of copper source is in the range of about 0.1-30 mole percent of copper based on hydroxyaromatic compound.
19. A method for preparing 4-bromophenol, 4-bromo-o-cresol or 4-bromo-m-cresol which comprises contacting phenol, o-cresol or m-cresol with air and hydrogen bromide in an acidic medium, in the presence of cupric bromide.
20. A method for converting a hydroxyaromatic compound to useful products which comprises:
 - (A) brominating said hydroxyaromatic compound to a p-brominated product in a first reaction vessel, and
 - (B) transferring said p-brominated product to a second reaction vessel and alternately
 - (1) hydrolyzing it to form a p-dihydroxyaromatic compound and
 - (2) reductively coupling it to form a dihydroxybiphenyl compound.

21. A method according to claim 20 wherein the hydroxyaromatic compound is phenol, o-cresol or m-cresol.

22. A method according to claim 21 wherein the hydroxyaromatic compound is phenol.

23. A method according to claim 20 wherein the product bromophenol compound is separated after step A.

24. A method according to claim 23 wherein separation is by distillation.

25. A method for converting a hydroxyaromatic compound selected from the group consisting of phenol, o-cresol and m-cresol which comprises:

(A) brominating said hydroxyaromatic compound in a first reaction vessel, and

(B) transferring the brominated product to a second reaction vessel and alternately (1) hydrolyzing it to form the corresponding dihydroxyaromatic compound and (2) reductively coupling it to form the corresponding dihydroxybiphenyl.

26. Apparatus for conducting chemical reactions, said apparatus comprising:

I. a first reaction vessel 2 adapted for the bromination of a hydroxyaromatic compound to a p-brominated product, and

II. a second reaction vessel 7 communicating directly or indirectly with said first vessel, said second vessel adapted for the alternate hydrolysis of said p-brominated product to a dihydroxyaromatic compound and reductive coupling of said p-brominated product to a dihydroxybiphenyl compound.

27. Apparatus according to claim 26 wherein each vessel 2 and 7 is a tank reactor.

28. Apparatus according to claim 26 wherein each vessel 2 and 7 is a continuous stirred tank reactor or a plug flow reactor.

29. Apparatus according to claim 26 further comprising agitators 3 and 10 in vessels I and II.

30. Apparatus according to claim 26 further comprising separation means 5 between said vessels I and II.

31. Apparatus for conducting chemical reactions, said apparatus comprising:

I. a first reaction vessel 2 which is a tank reactor fitted with agitator 3 and adapted for the bromination of phenol to 4-bromophenol;

II. a second reaction vessel 7 which is a tank reactor fitted with agitator 10 and communicating with said first vessel, said second vessel adapted for the alternate hydrolysis of said p-bromophenol to hydroquinone and reductive coupling of said p-bromophenol to 4,4'-dihydroxybiphenyl; and

III. separation means 5 between said vessels I and II.

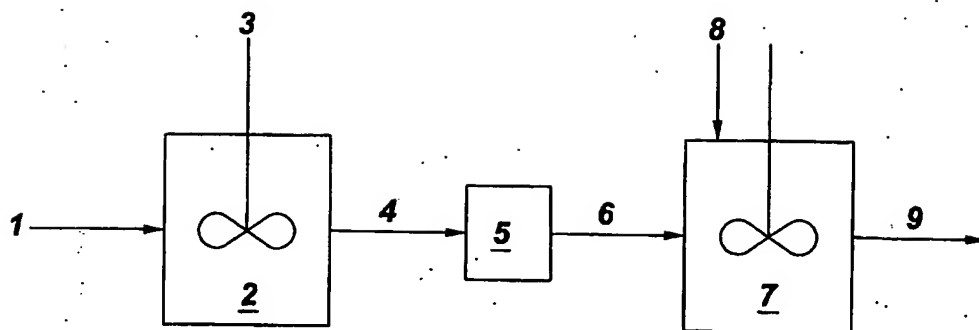
32. Apparatus for conducting chemical reactions, said apparatus comprising:

I. a first reaction vessel 2 which is a continuous tank reactor fitted with agitator 3 and adapted for the bromination of phenol to 4-bromophenol;

II. a second reaction vessel 7 which is a continuous tank reactor fitted with agitator 10 or a plug flow reactor and communicating with said first vessel, said second vessel adapted for the alternate hydrolysis of said p-bromophenol to hydroquinone and reductive coupling of said p-bromophenol to 4,4'-dihydroxybiphenyl; and

III. separation means 5 between said vessels I and II.

1/1

*Fig. 1*

CORRECTED VERSION

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
5 August 2004 (05.08.2004)

PCT

(10) International Publication Number
WO 2004/064695 A1

(51) International Patent Classification⁷: **C07C 37/62**,
37/02, 37/18, 39/27, 39/08, 39/15

(21) International Application Number:
PCT/US2003/041825

(22) International Filing Date:
18 December 2003 (18.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/342,475 16 January 2003 (16.01.2003) US

(71) Applicant (for all designated States except US): **GENERAL ELECTRIC COMPANY** [US/US]; 1 River Road, Schenectady, NY 12345 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PRESSMAN, Eric, James** [US/US]; 451 Miller Road, East Greenbush, NY 12061 (US). **OFORI, John, Yaw** [GH/US]; 1187 Hillside Avenue, Apt. B36, Niskayuna, NY 12309 (US). **SOLOVEICHIK, Grigori, Lev** [RU/US]; 37 Laura Drive, Latham, NY 12110 (US). **MILLS, Ryan, Christopher** [US/US]; 1402 Schooner Court, Clifton park, NY 12065 (US). **MALE, Jonathan, Lloyd** [GB/US]; 345 State Route 443, Shoharie, NY 12157 (US).

(74) Agents: **WINTER, Catherine, J. et al.**; Patent Counsel, General Electric Company, 3135 Easton Turnpike W3C, Fairfield, CT 06828 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(48) Date of publication of this corrected version:
28 October 2004

(15) Information about Correction:
see PCT Gazette No. 44/2004 of 28 October 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BROMINATION OF HYDROXYAROMATIC COMPOUNDS AND FURTHER CONVERSION TO DIHYDROXYAROMATIC COMPOUNDS

(57) Abstract: Brominated hydroxyaromatic compounds such as p-bromophenol are prepared by contacting a hydroxyaromatic compound with oxygen and a bromine source such as hydrogen bromide or an alkali metal or alkaline earth metal bromide in an acidic medium, in the presence of elemental copper or a copper compound as catalyst. The brominated product of this reaction may be converted alternately to a dihydroxyaromatic compound such as hydroquinone by hydrolyses, or a dihydroxybiphenyl compound such as 4,4'-dihydroxybiphenyl by reductive coupling.

WO 2004/064695 A1

BROMINATION OF HYDROXYAROMATIC COMPOUNDS AND FURTHER CONVERSION TO DIHYDROXYAROMATIC COMPOUNDS

BACKGROUND OF THE INVENTION

This invention relates to the reactions of hydroxyaromatic compounds; and more particularly to the conversion of such compounds to brominated derivatives, monocyclic dihydroxyaromatic compounds and dihydroxybiphenyls.

Monocyclic dihydroxyaromatic compounds such as hydroquinone and dihydroxybiphenyls such as 4,4'-dihydroxybiphenyl (hereinafter sometimes simply "biphenol") have numerous uses in the chemical industry. For example, both compounds can be used in polymer preparation, notably in the preparation of polycarbonates, polysulfones and polyimides, especially polyetherimides.

There are various methods for the preparation of hydroquinone and biphenol. As examples of such methods, each compound can be prepared from p-bromophenol, hydroquinone by hydrolysis and biphenol by reductive coupling in the presence of a noble metal catalyst, a base and a reducing agent.

Brominated hydroxyaromatic compounds, as exemplified by p-bromophenol, can be prepared by reaction of the precursor hydroxyaromatic compound with elemental bromine or with various kinds of bromides. For the most part, the use of hydrogen bromide alone is not successful. Auxiliary reagents are required; these may include oxidizing agents, reducing agents, catalysts and/or complexing agents. As a result, the commercial production of bromophenols by reaction of phenols with hydrogen bromide or other simple ionic bromides has, in general, not been pursued.

Normally, chemical plants are set up to produce a single product or group of products in a single reaction or a unitary sequence of reactions. It is thus possible to set up a single set of equipment and use it, on either a batch or continuous basis, permanently to produce the desired product.

Toll producers of chemicals, on the other hand, may utilize a wide variety of equipment, choosing individual items for use depending on the chemical then being produced. To vary the product, they may vary the connections between reactors so as to design a suitable set of equipment for the particular product.

So far as is presently known, the use of a unitary set of equipment to produce two or more widely diverse products is not a commercial alternative.

SUMMARY OF THE INVENTION

The present invention provides a facile method for the preparation of brominated hydroxyaromatic compounds using simple ionic bromides such as hydrobromic acid. Also provided is a method and apparatus for converting the brominated products thus prepared into two separate and diverse classes of chemicals, on an alternating basis. Thus, a first product may be synthesized as needed, after which a second product may be synthesized without any change in the equipment employed.

In a first aspect, the invention is a method for preparing a brominated hydroxyaromatic compound which comprises contacting a hydroxyaromatic compound with oxygen and a bromide source in an acidic medium, in the presence of elemental copper or a copper compound as catalyst.

A second aspect of the invention is a method for converting a hydroxyaromatic compound to useful products which comprises:

(A) brominating said hydroxyaromatic compound to a p-brominated product in a first reaction vessel, and

(B) transferring said p-brominated product to a second reaction vessel and alternately (1) hydrolyzing it to form a p-dihydroxyaromatic compound and (2) reductively coupling it to form a dihydroxybiphenyl compound.

A third aspect is apparatus for conducting chemical reactions, said apparatus comprising:

I. a first reaction vessel adapted for the bromination of a hydroxyaromatic compound to a p-brominated product, and

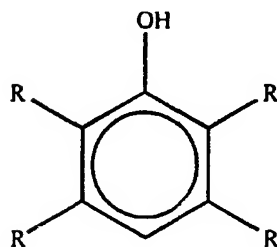
II. a second reaction vessel communicating directly or indirectly with said first vessel, said second vessel adapted for the alternate hydrolysis of said p-brominated product to a dihydroxyaromatic compound and reductive coupling of said p-brominated product to a dihydroxybiphenyl compound.

BRIEF DESCRIPTION OF THE DRAWING

The drawing is a block diagram of the apparatus of the invention.

DETAILED DESCRIPTION; PREFERRED EMBODIMENTS

The common initial reactant for all products obtained according to this invention is a hydroxyaromatic compound, preferably a monocyclic monohydroxyaromatic compound. It may be an unsubstituted hydroxyaromatic compound such as phenol, or a substituted compound provided, however, that the 4-position is unsubstituted and thus available for bromination. Preferred substituents (one or more) are alkyl groups, particularly C₁₋₄ alkyl. Illustrative compounds are those having the formula



wherein each R is independently hydrogen or a substituent, preferably C₁₋₄ alkyl.

Particularly preferred in most instances is phenol, and specific reference will be frequently made to phenol hereinafter. However, homologous compounds such as o- and m-cresol may be substituted for phenol as desired.

According to the first aspect of the invention, the phenol is contacted with oxygen and a bromine compound. The oxygen is employed in stoichiometric excess and may be pure oxygen or may be employed in the form of air or oxygen-enriched air; ordinary air is often preferred. Contact may be with flowing oxygen or air or under pressure, typically up to about 100 atm.

Suitable bromine compounds include hydrogen bromide and bromide salts. Hydrogen bromide may be employed in any form; examples are gaseous HBr, aqueous HBr (hydrobromic acid) and HBr in solution in a polar organic solvent, typically one of the solvents described hereinafter. Bromide salts include alkali metal bromides such as sodium bromide and potassium bromide and alkaline earth metal bromides such as calcium bromide and magnesium bromide. Hydrobromic acid is generally the preferred bromine compound. It may be employed at any concentration, including the commercially available 48% (by volume) aqueous solution.

Said contact is in an acidic medium. Aqueous acidic media including Brønsted acids generally, and particularly including sulfuric acid, phosphoric acid and nitric acid, may be employed; or, if hydrobromic acid is the bromine compound employed, it may serve as the acidic medium. Polar organic solvents may also be present. These may include polar aprotic solvents such as acetonitrile, dimethyl sulfoxide, chloroform and o-dichlorobenzene, as well as protic solvents such as water, acetic acid and excess hydroxyaromatic compound. Acetic acid and acetonitrile are frequently preferred. Mixtures of the foregoing solvents may be employed. It is often preferred that the reaction medium be anhydrous.

Said contact is also in the presence of elemental copper or a copper compound as a catalyst of the bromination reaction. Copper compounds are generally preferred. Examples are cupric sulfate, cupric chloride, cupric bromide, cuprous chloride and cuprous bromide. Cupric bromide is often preferred by reason of its relatively low cost and particular suitability, as contact with hydrobromic acid will usually convert other cupric salts to the bromide.

The bromination reaction may be conducted at a temperature in the range of about 20-150°C, preferably about 60-80°C. Proportions of copper source are most often in the range of about 0.1-30 mole percent of copper based on hydroxyaromatic compound. The molar ratio of ionic bromide to hydroxyaromatic compound is preferably less than 1:1, to minimize conversion to dibromo and more highly brominated compounds; ratios in the range of about 0.2-0.9:1 are typical.

The product of the bromination reaction is usually predominantly the p-bromo compound, with minor amounts of o-bromo compound and dibromo and higher

compounds also being present. Conversion of phenol to bromophenols is, for the most part, at least 40%, "conversion" being defined as total phenol (in weight units or moles) consumed as a percentage of phenol originally present. Selectivity to 4-bromophenol is usually at least 80% and often greater than 90%, "selectivity" meaning moles of the specific product formed as a percentage of moles of phenol consumed.

Separation of the bromophenol compounds prepared according to the invention may be effected by art-recognized methods. Distillation is generally preferred, since there is a difference of more than 40°C between the boiling points of 2-bromophenol (194.5°C) and 4-bromophenol (238°C) and the dibromophenols have even higher boiling points. Distillation may be conducted under reduced pressure to minimize thermal decomposition.

According to the second aspect of the invention, a bromination reaction, which may preferably be but need not be the reaction of the first aspect, is conducted in a first reaction vessel, which may be a conventional tank reactor as used in a batch process or a continuous stirred tank reactor (CSTR) as used in a continuous process. When necessary or appropriate, the bromination product mixture may be transferred from said first vessel to appropriate separation means. The p-brominated product is thence transferred to a second reaction vessel, which may also be a tank reactor or CSTR, for performance of the second step.

The key feature of this aspect is the performance alternately of the hydrolysis and reductive coupling steps. These are alternated as desired to produce the currently desired product; by "alternately" is meant that the hydrolysis and reductive coupling operations are performed in succession as required by product necessities, with switching between the two operations when needed. Both the hydrolysis and the reductive coupling steps may be performed batchwise or continuously, as described hereinabove for the bromination step.

For hydrolysis to a dihydroxyaromatic compound such as hydroquinone (aspect B-1), the bromophenol is contacted with an aqueous base in the presence of a suitable catalyst, typically elemental copper or an oxide thereof, at a temperature of at least

about 75°C and preferably in the range of about 75-150°C. Illustrative conditions are those described in any part of US Patent 1,934,656, the disclosure of which is incorporated by reference herein.

For reductive coupling to a dihydroxybiphenyl compound such as biphenol (aspect B-2), the bromophenol is contacted with a reducing agent such as formic hydrazide in the presence of an aqueous base and a platinum group catalyst, preferably palladium which may be supported on carbon. This reaction may be carried out at temperatures similar to those of the hydrolysis step, typically in the range of about 60-100°C. US Patent 5,177,258 is incorporated by reference herein for its disclosure of typical conditions for the reductive coupling reaction.

A notable feature of reactions B-1 and B-2 is the similarity of the conditions under which they are performed. Both require relatively low temperatures, no higher in general than about 150°C. Both employ aqueous base, most often an alkali metal hydroxide and a metal-containing catalyst. Both can be conducted in either a glass or a metal reaction vessel; if a vessel comprising copper is used for hydrolysis, it may provide enough of that metal to serve as a catalyst.

Thus, it is possible to use the second vessel for either hydrolysis or reductive coupling, with little or no alteration other than cleaning before changing from one reaction to the other. This has the advantage of making it possible to conduct the hydrolysis and reductive coupling reactions on an alternating basis.

Reference is now made to the drawing to help explain the apparatus of the invention. Phenol, hydrobromic acid, copper compound and any solvent employed are introduced at 1 into first reaction vessel 2, which may be a tank reactor, a CSTR, a plug flow reactor or the like. The reactants may be introduced through separate lines or premixed and introduced through a single line.

In vessel 2, the reactants are brought into contact and mixed with the aid of agitator 3, under conditions for preparation of bromophenols. When the reaction has reached substantial completion, the product is withdrawn at 4 and passed into optional separation (e.g., distillation) means 5, where the constituents of the product are

separated and the desired constituent, usually 4-bromophenol, is passed at 6 into second reaction vessel 7 which is equipped with agitator 10.

Depending on the product desired, the constituent introduced at 6 may be contacted at 8 with aqueous base and a copper-containing catalyst under conditions for hydrolysis of bromophenol to hydroquinone, which is removed at 9. When the need for production of hydroquinone has been met, vessel 7 may be cleaned and introduction of constituent at 6 resumed, while reducing agent, aqueous base and platinum group catalyst are introduced at 8. Conditions are established for the reductive coupling of bromophenol to biphenol and its removal at 9. Other equipment suitable for purification of hydroquinone or biphenol may be fed at 9 from vessel 7.

The invention is illustrated by the following examples. All percentages are by weight.

EXAMPLE 1

To a 3-dram vial were charged 1.37 ml (15.56 mmol) of phenol, 0.112 g (0.5 mmol) of cupric bromide, 1.39 ml (12.50 mmol) of 48% hydrobromic acid and 2.20 ml of acetonitrile. The vial was sealed with a cap containing a hole to allow for air flow during the reaction and placed in an aluminum block. The block was placed in a 450-ml autoclave reactor, pressurized to 34.0 atm with air and heated at 65° C for 1 hour. It was then cooled to room temperature and depressurized. The resulting mixture was analyzed by vapor phase chromatographic analysis and shown to contain 7.39% phenol, 28.63% 4-bromophenol, 5.59% 2-bromophenol and 0.68% 2,4-dibromophenol, corresponding to 72% phenol conversion, with 82% 4-bromophenol selectivity and a total monobromophenol selectivity of 98%.

EXAMPLE 2

To a 3-dram vial were charged 1.59 ml (15.39 mmol) of o-cresol, 0.112 g (0.5 mmol) of cupric bromide, 1.48 ml (12.47 mmol) of 48% hydrobromic acid and 1.92 ml of acetonitrile. The vial was sealed and located as in Example 1, pressurized to 34.0 atm with air and heated at 65° C for 1 hour. It was then cooled to room temperature and depressurized. The resulting mixture was analyzed by vapor phase chromatographic analysis and shown to contain 13.23% o-cresol, 27.74% 4-bromo-2-methylphenol and

0.93% 6-bromo-2-methylphenol, corresponding to 56% o-cresol conversion, with 96% 4-bromo-2-methylphenol selectivity and a total monobromophenol selectivity of 99%.

EXAMPLE 3

To a 3-dram vial were charged 1.37 ml (15.56 mmol) of phenol, 0.112 g (0.5 mmol) of cupric bromide, 1.30 ml (6.85 mmol) of a 30% solution of hydrogen bromide in acetic acid and 2.31 ml of acetonitrile. The vial was sealed and located as in Example 1, pressurized to 34.0 atm with air and heated at 65° C for 1 hour. It was then cooled to room temperature and depressurized. The resulting mixture was analyzed by vapor phase chromatographic analysis and shown to contain 14.12% phenol, 19.15% 4-bromophenol and 1.15% 2-bromophenol, corresponding to 44% phenol conversion, with 96% 4-bromophenol selectivity and a total monobromophenol selectivity of 100%.

EXAMPLE 4

An apparatus as shown in the drawing is employed, with each of vessels 2 and 7 being a tank reactor. In vessel 2, the procedure of Example 3 is performed in amounts suitable for commercial production on reagents introduced separately at 1. The product is withdrawn at 4 and distilled in distillation apparatus 5. The 4-bromophenol recovered by distillation is passed at 6 into vessel 7 fabricated of copper.

In a first run, aqueous sodium hydroxide solution is introduced at 8 and the conditions described in Example 1 of US Patent 1,934,656 are maintained. The hydroquinone obtained as product is worked up and isolated as in that example.

EXAMPLE 5

In a second run following the preparation and isolation of 4-bromophenol as in Example 4, a coupling reaction to produce biphenol is performed in accordance with the general disclosure of US Patent 5,177,258. The reaction employs 1 part of 4-bromophenol in vessel 7 and 2.5 parts of sodium hydroxide, 0.6 part of palladium catalyst (5% by weight on carbon) and 3 parts of formic hydrazide in water, introduced at 8.

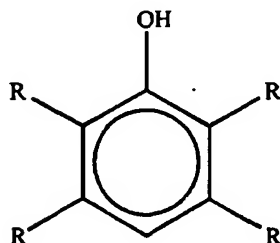
While typical embodiments have been set forth for the purpose of illustration, the foregoing descriptions and examples should not be deemed to be a limitation on the scope of the invention. Accordingly, various modifications, adaptations, and alternatives may occur to one skilled in the art without departing from the spirit and scope of the present invention

What is claimed is:

1. A method for preparing a brominated hydroxyaromatic compound which comprises contacting a hydroxyaromatic compound with oxygen and a bromine compound selected from the group consisting of hydrogen bromide and ionic bromide salts in an acidic medium, in the presence of elemental copper or a copper compound as catalyst.

2. A method according to claim 1 wherein said medium is anhydrous.

3. A method according to claim 1 wherein the hydroxyaromatic compound has the formula



wherein each R is independently hydrogen or C₁₋₄ alkyl.

4. A method according to claim 1 wherein the hydroxyaromatic compound is phenol, o-cresol or m-cresol.

5. A method according to claim 4 wherein the hydroxyaromatic compound is phenol.

6. A method according to claim 4 wherein the hydroxyaromatic compound is o-cresol.

7. A method according to claim 1 wherein the bromine compound is hydrogen bromide.

8. A method according to claim 1 wherein the oxygen is provided by air.

9. A method according to claim 1 wherein the copper is provided as cupric bromide, cupric sulfate, cupric chloride, cuprous chloride or cuprous bromide.

10. A method according to claim 9 wherein the copper is provided as cupric bromide.
11. A method according to claim 1 wherein flowing oxygen is employed.
12. A method according to claim 1 wherein oxygen under pressure is employed.
13. A method according to claim 1 wherein a polar organic solvent is also present.
14. A method according to claim 1 wherein the solvent is acetonitrile, dimethyl sulfoxide, chloroform, o-dichlorobenzene, water, phenol, o-cresol, m-cresol, propionic acid or acetic acid.
15. A method according to claim 14 wherein the solvent is acetonitrile or acetic acid.
16. A method according to claim 1 wherein a temperature in the range of about 20-150°C is employed.
17. A method according to claim 1 wherein a molar ratio of ionic bromide to hydroxyaromatic compound less than 1:1 is employed.
18. A method according to claim 1 wherein the proportion of copper source is in the range of about 0.1-30 mole percent of copper based on hydroxyaromatic compound.
19. A method for preparing 4-bromophenol, 4-bromo-o-cresol or 4-bromo-m-cresol which comprises contacting phenol, o-cresol or m-cresol with air and hydrogen bromide in an acidic medium, in the presence of cupric bromide.
20. A method for converting a hydroxyaromatic compound to useful products which comprises:
 - (A) brominating said hydroxyaromatic compound to a p-brominated product in a first reaction vessel, and
 - (B) transferring said p-brominated product to a second reaction vessel and alternately
 - (1) hydrolyzing it to form a p-dihydroxyaromatic compound and
 - (2) reductively coupling it to form a dihydroxybiphenyl compound.

21. A method according to claim 20 wherein the hydroxyaromatic compound is phenol, o-cresol or m-cresol.
22. A method according to claim 21 wherein the hydroxyaromatic compound is phenol.
23. A method according to claim 20 wherein the product bromophenol compound is separated after step A.
24. A method according to claim 23 wherein separation is by distillation.
25. A method for converting a hydroxyaromatic compound selected from the group consisting of phenol, o-cresol and m-cresol which comprises:
 - (A) brominating said hydroxyaromatic compound in a first reaction vessel, and
 - (B) transferring the brominated product to a second reaction vessel and alternately (1) hydrolyzing it to form the corresponding dihydroxyaromatic compound and (2) reductively coupling it to form the corresponding dihydroxybiphenyl.
26. Apparatus for conducting chemical reactions, said apparatus comprising:
 - I. a first reaction vessel 2 adapted for the bromination of a hydroxyaromatic compound to a p-brominated product, and
 - II. a second reaction vessel 7 communicating directly or indirectly with said first vessel, said second vessel adapted for the alternate hydrolysis of said p-brominated product to a dihydroxyaromatic compound and reductive coupling of said p-brominated product to a dihydroxybiphenyl compound.
27. Apparatus according to claim 26 wherein each vessel 2 and 7 is a tank reactor.
28. Apparatus according to claim 26 wherein each vessel 2 and 7 is a continuous stirred tank reactor or a plug flow reactor.
29. Apparatus according to claim 26 further comprising agitators 3 and 10 in vessels I and II.

30. Apparatus according to claim 26 further comprising separation means 5 between said vessels I and II.

31. Apparatus for conducting chemical reactions, said apparatus comprising:

I. a first reaction vessel 2 which is a tank reactor fitted with agitator 3 and adapted for the bromination of phenol to 4-bromophenol;

II. a second reaction vessel 7 which is a tank reactor fitted with agitator 10 and communicating with said first vessel, said second vessel adapted for the alternate hydrolysis of said p-bromophenol to hydroquinone and reductive coupling of said p-bromophenol to 4,4'-dihydroxybiphenyl; and

III. separation means 5 between said vessels I and II.

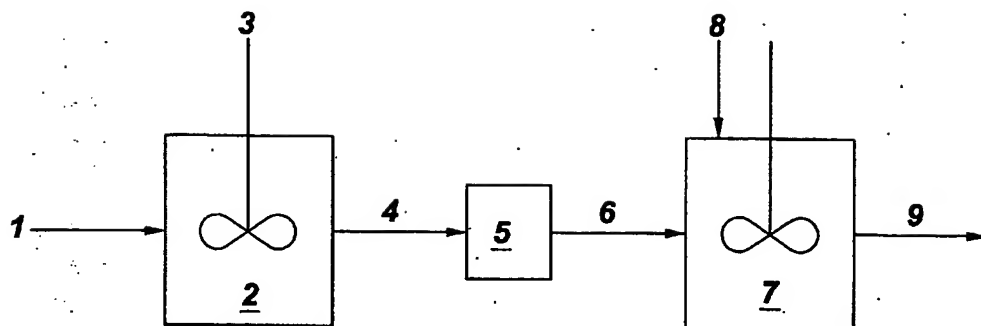
32. Apparatus for conducting chemical reactions, said apparatus comprising:

I. a first reaction vessel 2 which is a continuous tank reactor fitted with agitator 3 and adapted for the bromination of phenol to 4-bromophenol;

II. a second reaction vessel 7 which is a continuous tank reactor fitted with agitator 10 or a plug flow reactor and communicating with said first vessel, said second vessel adapted for the alternate hydrolysis of said p-bromophenol to hydroquinone and reductive coupling of said p-bromophenol to 4,4'-dihydroxybiphenyl; and

III. separation means 5 between said vessels I and II.

1/1

*Fig. 1*

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/41825

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C37/62 C07C37/02 C07C37/18 C07C39/27 C07C39/08
C07C39/15

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2 805 263 A (LINDBLOM ROBERT O ET AL) 3 September 1957 (1957-09-03) claims 1,3,5,6; examples 3,4	1-19
Y	US 3 796 732 A (BRENNER W) 12 March 1974 (1974-03-12) abstract; claims; examples 6,10,11,13	1-25
Y	KÖLBEL, M. ET AL.: "Thermotropic and lyotropic liquid crystalline phases of rigid aromatic amphiphiles" CHEM. EUR. J., vol. 6, no. 20, 2000, pages 3821-3837, XP001181740 page 3831, column 2, last paragraph -/-	1-19

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

16 August 2004

Date of mailing of the international search report

10. 09. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kiernan, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/41825

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>NARENDER N ET AL: "AN EFFICIENT AND REGIOSELECTIVE OXYBROMINATION OF AROMATIC COMPOUNDS USING POTASSIUM BROMIDE AND OXONE"</p> <p>SYNTHETIC COMMUNICATIONS, MARCEL DEKKER, NEW YORK, NY, US, vol. 32, no. 15, August 2002 (2002-08), pages 2313-2318, XP001143706 ISSN: 0039-7911 page 2314 - page 2315; table 1</p>	1-19
A	<p>US 1 934 656 A (BASS SHAILER L ET AL) 7 November 1933 (1933-11-07) claims; examples</p>	20-25
A	<p>EP 0 514 821 A (BROMINE COMPOUNDS LTD) 25 November 1992 (1992-11-25) the whole document</p>	20-25
Y	<p>US 1 907 246 A (BRITTON EDGAR C ET AL) 2 May 1933 (1933-05-02) claims; examples</p>	20-25
A	<p>EP 0 206 543 A (ICI PLC) 30 December 1986 (1986-12-30) page 8; example 14</p>	20-25

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/41825

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 26-32
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 26-32

Claims 26-32 are directed to an apparatus consisting of a first reaction vessel "adapted for the bromination" and a second reaction vessel "adapted for the alternate hydrolysis ... and reductive coupling...". However, these expressions are not appropriate apparatus features and are not considered limiting for the apparatus claims. As a consequence, no meaningful search could be carried out for the apparatus claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 03/41825

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2805263	A	03-09-1957	NONE	
US 3796732	A	12-03-1974	CH 566280 A5	15-09-1975
			BE 783512 A1	16-11-1972
			CA 961498 A1	21-01-1975
			CS 161656 B2	10-06-1975
			DD 98906 A5	12-07-1973
			DE 2221624 A1	30-11-1972
			DK 134316 B	18-10-1976
			FR 2138030 A5	29-12-1972
			GB 1364796 A	29-08-1974
			HU 163555 B	27-09-1973
			IE 36360 B1	13-10-1976
			IL 39225 A	28-07-1975
			JP 53017585 B	09-06-1978
			NL 7205525 A ,B	21-11-1972
			PL 88994 B1	30-10-1976
			RO 68938 A1	01-02-1982
			SE 396070 B	05-09-1977
			SU 474133 A3	14-06-1975
			ZA 7202442 A	31-01-1973
			AU 461525 B2	29-05-1975
			AU 4112272 A	18-10-1973
US 1934656	A	07-11-1933	NONE	
EP 0514821	A	25-11-1992	IL 98209 A	27-11-1995
			DE 69215001 D1	12-12-1996
			DE 69215001 T2	10-04-1997
			EP 0514821 A1	25-11-1992
			JP 5178790 A	20-07-1993
			US 5177258 A	05-01-1993
US 1907246	A	02-05-1933	NONE	
EP 0206543	A	30-12-1986	EP 0206543 A2	30-12-1986
			JP 61293932 A	24-12-1986
			US 4851538 A	25-07-1989

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.